Testing Epinephrine for Out-of-Hospital Cardiac Arrest

Clifton W. Callaway, M.D., Ph.D., and Michael W. Donnino, M.D.

The administration of epinephrine has been part of the resuscitation of patients with cardiac arrest since the 1960s. The rationale for the use of epinephrine includes evidence from studies in animals and from clinical trials in humans that increasing vasomotor tone during circulatory collapse and chest compressions improves coronary perfusion pressure, shunts more blood to the heart, and increases the likelihood of restoring spontaneous circulation. However, epinephrine also decreases microvascular blood flow in some organs, increases cardiac dysrhythmias, and increases myocardial oxygen demand during critical ischemia. These deleterious effects can result in long-term organ dysfunction or hypoperfusion of the heart and brain. Despite decades of epinephrine use, data on the benefit of the drug comes primarily from conflicting observational studies with a high risk of bias.

The PARAMEDIC2 trial reported now in the Journal provides the largest set of randomized data on epinephrine use in out-of-hospital cardiac arrest so far. In this trial, patients with cardiac arrest were randomly assigned to receive parenteral epinephrine or saline, with trial-group assignments concealed from both the treating teams and the outcome assessors. All but 7 of 8014 patients were included in the primary analysis at 30 days. Groups were well balanced with respect to most baseline characteristics. These features greatly reduced the risk of bias, and this pragmatic trial provides the most rigorous data on patient-centered outcomes with respect to epinephrine to date.

Patients who received epinephrine had a higher rate of 30-day survival than those who received placebo (adjusted odds ratio, 1.47; 95% confidence interval [CI], 1.09 to 1.97), but the overall survival rate in this trial was disappointingly small (3.2% and 2.4%, respectively). There was no clear improvement in functional recovery among the survivors in the epinephrine group as compared with the placebo group (adjusted odds ratio, 1.19; 95% CI, 0.85 to 1.68), and the proportion of survivors with severe neurologic impairment was actually higher in the epinephrine group (31.0% vs. 17.8%), which raised concern that some of the additional survivors did not have a desirable quality of life. Epinephrine robustly improved a return of spontaneous circulation (36.3% vs. 11.7%), a finding that was consistent with the results of observational studies and with a previous smaller randomized trial (adjusted odds ratio, 3.4; 95% CI, 2.0 to 5.6). The small magnitude of the higher rate of survival and absence of functional recovery will prompt debate about whether epinephrine is truly beneficial for improving meaningful clinical outcomes.

One major limitation of the trial is that the protocol neither controlled nor measured in-hospital treatments. The most common cause of in-hospital death is iatrogenic limitation of life support, which may result in the death of potentially viable patients. Conversely, treating teams may work harder to treat or reduce injury in the sickest patients in the intensive care unit, thereby minimizing differences created by prehospital therapy. Measuring or regimenting hospital care is both difficult and expensive, but some trials have shown that it is possible. The success of those trials supports the inclusion of such data or protocols as a standard part of any trial involv-
The benefits of the use of epinephrine during cardiac arrest may depend on timing, initial electrocardiographic rhythm, and dose. With regard to timing, paramedics administered the trial agent a median of 21 minutes after the emergency call, which is slightly longer than the interval in other out-of-hospital trials. This timing is dramatically different for in-hospital cardiac arrest, where epinephrine is administered a median of 3 minutes after resuscitation starts, and the results should not be extrapolated to this setting. Effects of very early epinephrine administration in out-of-hospital arrest remain unknown and may be impossible to test with current delivery systems.

Epinephrine increased 30-day survival in patients with nonshockable rhythms (adjusted odds ratio, 2.15; 95% CI, 1.13 to 4.09) but had unclear benefit in those with shockable rhythms (adjusted odds ratio, 1.33; 95% CI, 0.95 to 1.86). Rapid epinephrine use is associated with better outcomes in patients with nonshockable rhythms during in-hospital cardiac arrest, but early administration immediately after the first rescue shock is associated with worse outcomes in patients with shockable rhythms. Shockable rhythms are more likely to occur in patients with cardiac or cardiovascular causes of arrest, which epinephrine may exacerbate. The data support the principle that drug administration should not compete with or delay defibrillation and that epinephrine may have different effects in patients with different electrocardiographic rhythms.

The mean (±SD) total dose of epinephrine in this trial was 4.9±2.5 mg. Higher epinephrine doses produce much smaller incremental increases in return of spontaneous circulation and do not improve long-term survival. These results do not encourage studying higher epinephrine doses but suggest that it would be desirable to have more data on whether smaller doses of epinephrine could promote a return of spontaneous circulation with fewer adverse effects.

Despite having a powerful effect on restoring spontaneous circulation after out-of-hospital cardiac arrest, epinephrine produced only a small absolute increase in survival with no increase in favorable functional recovery as compared with placebo. We now must ponder whether additional treatments after a return of spontaneous circulation could improve functional recovery, whether drug use should differ on the basis of cardiac rhythm, and whether lower doses of epinephrine would be superior to higher doses among patients with out-of-hospital cardiac arrest.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

From the University of Pittsburgh, Pittsburgh (C.W.C.); and Beth Israel Deaconess Medical Center, Boston (M.W.D.).

This editorial was published on July 18, 2018, at NEJM.org.


DOI: 10.1056/NEJMe1808255
Copyright © 2018 Massachusetts Medical Society.